

## REMARKS

Initially, the Examiner has again rejected claims 40-57 under 35 U.S.C. 103(a) as being obvious and, therefore, unpatentable over Kirschner et al. U.S. Patent No. 6,899,890 ("Kirschner") in combination with Herschler U.S. Patent No. 4,997,823 ("Herschler") and Kelly International Patent Publication No. WO 02/092097 ("Kelly"). The Examiner makes clear that Kirschner discloses a vaginal drug delivery method suitable for delivery of therapeutic active drugs, including antibacterial agents such as azithromycin or metronidazole. However, the Examiner acknowledges that Kirschner does not disclose the administration of an antibiotic, such as azithromycin, in combination with a prostaglandin. Similarly, Kelly discloses the delivery, via injection, of a prostaglandin, such as misoprostol, directly to the cervix or via the vaginal fornix. However, Kelly also does not disclose the administration of an antibiotic in combination with the prostaglandin. It is only in Herschler that a combination of an antibiotic and prostaglandin is disclosed, but the combination is not administered vaginally. Nevertheless, the Examiner continues to assert that it would have been obvious to one of skill in the art to administer vaginally, a combination of an antibiotic in combination with prostaglandin "because a person would have expected that the resulting combination would be effective in treating prostaglandin (sic) [in] the vagina." Office Action, May 20, 2010, paragraph bridging pages 2 and 3.

While the Applicant has continued to argue that co-administration of an antibiotic and prostaglandin provides a synergistic effect in the treatment of pelvic infections and in reducing surgical traumas, which synergistic effect is not found in the administration of each ingredient by itself, the Examiner has countered that this argument is not persuasive, indicating that the terminology of claims 40 and 44 "encompasses a combination of any antibiotic with azithromycin in any proportion and a combination of (sic) any prostaglandin with misoprostol in any proportion." Office Action, May 20, 2010, last paragraph of page 3. Further, according to the Examiner, data showing the administration of 500 mg of azithromycin and 200 mcg of misoprostol is not commensurate with the scope of former claims 56 and 57, which administer about 250 to about 1000 milligrams of azithromycin and about 50 to about 1000 milligrams of misoprostol.

In response, Applicant has amended claims 40 and 44 by including the limitations set forth in claims 56 and 57, respectively. The claims now limit the vaginal administration of a therapeutically effective amount of an antibiotic and of a prostaglandin to, from about 250 milligrams to about 1000 milligrams of azithromycin as the antibiotic and from about 50 to about 1000 milligrams of misoprostol as the prostaglandin. This limitation has been shown in the present application to have a synergistic effect in the treatment of pelvic infections and in reducing surgical traumas, no found where the antibiotic or prostaglandin are administered by themselves. Further, contrary to the Examiner's remarks, there is ample evidence to support this proposition in the application. In addition, in further support of the inventive nature of the invention, Applicant has attached herewith as Exhibit A in the Appendix, a Declaration of the inventor, Dr. Hazem El-Refaey, wherein it is expressly averred that administering vaginally a therapeutically effective amount of from 250 milligrams to about 1000 milligrams of azithromycin and from 50 milligrams to about 1000 milligrams of misoprostol results in a synergistic effect between these two drugs leading to the improved treatment of pelvic tissue infection and the reduction of surgical traumas resulting from gynaecological operation. Moreover, Dr. El-Refaey further avers that this synergistic effect is achieved throughout the entire range of amounts of azithromycin and misoprostol. Thus, the highest amounts of the two drugs in combination will provide a synergistic effect, as well as the lowest amounts of the two drugs in combination, and any combination in between.

In addition to the above, Dr. El-Refaey indicates how a synergistic effect is created by the combination of the misoprostol and azithromycin. Notably, using the synergistic nature of the combination, high levels of azithromycin are found in the target tissue compared to administration of azithromycin alone. None of the prior art provide for such a synergistic effect.

Thus, while Applicant continues to find it hard to believe the Examiner continues to assert that it would have been obvious to vaginally administer an azithromycin and a prostaglandin in combination based upon the prior art cited, Applicant believes the limitation of the prostaglandin to misoprostol, the antibiotic to azithromycin and the limitation of the amounts of each, together with the clear evidence of the synergistic effect

provided by the combination for pelvic tissue infections and surgical traumas, clearly distinguishes the claims from the cited prior art. One of ordinary skill in the art would clearly have not been motivated to select the claimed species of antibiotic and the claimed species of prostaglandin, in combination, and in the amounts to obtain the claimed invention, as required in order to establish a *prima facie* case of obviousness (see M.P.E.P. §2144.08 (II)(A)(4)).

Again, neither Herschler nor Kelly discloses the vaginal administration of azithromycin. While the Examiner alleges that Kirschner discloses the vaginal administration of azithromycin, and combines it with Herschler and Kelly, which are alleged to teach the vaginal administration of prostaglandin, Applicants respectfully disagree one of ordinary skill in the art would find it obvious that the synergistic effect produced by the administration of both azithromycin and misoprostol would have been obvious to one of ordinary skill in the art. Any such effect would have not been reasonably predictable, firstly, on the basis that the effect of a combination of azithromycin with a prostaglandin both administered vaginally had never been done before and, secondly, on the basis that the prior art teaches so many possible combinations of ingredients to be administered vaginally, that limiting the invention to the vaginal administration of azithromycin and misoprostol would not have been considered by any person of ordinary skill in art.

As previously noted in prior responses, Kirschner refers to a long list of many therapeutically active drugs for administration such as antifungal agents, antiviral agents, spermicides, surface active drugs, androgenic substances, for use with a wide selection of delivery systems such as dispersions, solids, suspensions, ointments, pastes, powders, foams, creams, jellies, sprays, gels, tablets, sponges and patches. Reference to azithromycin in Kirschner is limited to a passing mention in a long list of many other antibacterial agents as part of a larger list of many therapeutically active drugs. Moreover, there is no mention of prostaglandin or misoprostol. Similarly, misoprostol is only listed as one of several examples of a prostaglandin in Kelly. There are so many possible combinations of ingredients that could have been administered based upon a combination of Kirschner and

either Herschler or Kelly, that one of skill in the could not have reasonably predicted the result uncovered by the Applicant.

Thus, considering the express teaching of the references, one of ordinary skill in the art would not have been able to combine the references to provide for the administration of azithromycin vaginally with misoprostol, in the amounts now provided, in order to treat various pelvic infections. There is simply no teaching or suggestion of that in any of the references and/or in any combination of the references, that azithromycin and misoprostol can be administered vaginally. Even if the Examiner takes the position that Kirschner et al. provides for the vaginal administration of azithromycin, it does not provide for the vaginal administration of BOTH azithromycin and misoprostol. Simply asserting that it would have been obvious to do so can only be done in hindsight and would not be viewed by one of skill in the art as “predictable” prior to Applicant’s invention.

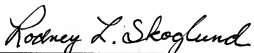
It has been found in the present invention that co-administration of an antibiotic, namely azithromycin, and a prostaglandin, namely misoprostol, or administration of misoprostol followed by azithromycin, is advantageous because of a synergistic effect between the antibiotic and prostaglandin as disclosed in the application and now further supported by the Declaration of Dr. El-Refaey. In this way, the collagenolytic properties of misoprostol helps to break apart collagen in the tissue at the site of administration and allows for easier absorption of the azithromycin into the target tissue. Thus, the treatment of pelvic tissue infection is improved. Nowhere is this affect shown in any of the prior art and, given the area of infection and the ingredients employed, it would not have been predictable.

Furthermore, the Examiner has made no express findings of fact that would have lead to his contention that the combination of the prior art supports a *prima facie* case of obviousness. See M.P.E.P. §2144.08 (II)(A)(4)(f). The Examiner’s bald assertion that a person would have expected that the resulting combination would be effective in treating pelvic infections in the vagina, has no basis of support. Moreover, it is completely inaccurate to the extent that it asserts an unreasonable expectation. One of skill in the art would not have expected this result.

In light of the foregoing, reconsideration of all pending claims 40-55 is respectfully requested, and a Notice of Allowance of those claims is earnestly solicited. Should the Examiner wish to discuss any of the foregoing in greater detail, the undersigned attorney would welcome a telephone call.

In the event that a fee required for the filing of this document is missing or insufficient, the undersigned attorney hereby authorizes the Commissioner to charge payment of any fees associated with this communication or to credit any overpayment to Deposit Account No. **18-0987**.

Respectfully submitted,

  
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Rodney L. Skoglund, Reg. No. 36,010  
Renner, Kenner, Greive, Bobak, Taylor & Weber  
Fourth Floor, First National Tower  
Akron, Ohio 44308-1456  
Telephone: (330) 376-1242  
Attorney for Applicant

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